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Abstract: Little is known regarding alterations of the renin-angiotensin system in patients referred for cardiac catheterization. Here, we measured plasma levels of active renin and aldosterone in patients referred for cardiac catheterization in order to determine the prevalence of elevated renin, aldosterone, and the aldosterone-renin ratio.A chemiluminescence assay was used to measure plasma aldosterone concentration (PAC) and active renin levels in 833 consecutive patients, after an overnight fasting and without any medication for least 12 hours. We evaluated associations of the hormonal elevations in relation to hypertension, atrial fibrillation (AF), hypertensive cardiomyopathy, coronary artery disease (CAD), valvular disease, impaired left ventricular ejection fraction (LVEF < 35%), and pulmonary hypertension (arterial pulmonary mean pressure >25 mm Hg).Hyperaldosteronism occurred in around one-third of all examined patients, without significant differences between patients with or without the named cardiac diseases. In a comparison between patients with or without any given cardiac disease condition, renin was significantly elevated in patients with either hypertension (36.4% vs 15.9%), CAD (33.9% vs 22.1%), or impaired LVEF (47.3% vs 24.8%). The angiotensin-renin ratio was elevated in AF patients and in patients with hypertensive cardiomyopathy. Patients with AF and coexisting hypertension had elevated renin more frequently than AF patients without coexisting hypertension (35.3% vs 16.5%; P = .005). Patients with persistent/permanent AF more frequently had elevated renin than patients with paroxysmal AF (34.1% vs 15.8%; P = .007).This prospective study of consecutive cardiac disease patients referred for cardiac catheterization has revealed distinct cardiac disease condition-associated differences in the frequencies of elevations in plasma renin, PAC, and the aldosterone-renin ratio.

DOI: https://doi.org/10.1097/MD.0000000000007282

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Abstract

Little is known regarding alterations of the renin-angiotensin system in patients referred for cardiac catheterization. Here, we measured plasma levels of active renin and aldosterone in patients referred for cardiac catheterization in order to determine the prevalence of elevated renin, aldosterone, and the aldosterone-renin ratio.

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Hyperaldosteronism occurred in around one-third of all examined patients, without significant differences between patients with or without the named cardiac diseases. In a comparison between patients with or without any given cardiac disease condition, renin was significantly elevated in patients with either hypertension (36.4% vs 15.9%), CAD (33.9% vs 22.1%), or impaired LVEF (47.3% vs 24.8%). The angiotensin-renin ratio was elevated in AF patients and in patients with hypertensive cardiomyopathy. Patients with AF and coexisting hypertension had elevated renin more frequently than AF patients without coexisting hypertension (35.3% vs 16.5%; $P = .005$). Patients with persistent/permanent AF more frequently had elevated renin than patients with paroxysmal AF (34.1% vs 15.8%; $P = .007$).

This prospective study of consecutive cardiac disease patients referred for cardiac catheterization has revealed distinct cardiac disease condition-associated differences in the frequencies of elevations in plasma renin, PAC, and the aldosterone-renin ratio.

Abbreviations: AF = atrial fibrillation, ARR = aldosterone-renin ratio, AVS = adrenal vein sampling, CAD = coronary artery disease, IQR = interquartile ranges, LV = left ventricular, LVEF = left ventricular ejection fraction, PAC = plasma aldosterone concentration.

Keywords: aldosterone, aldosterone-renin ratio, atrial fibrillation, coronary artery disease, pulmonary artery pressures, reduced LVEF, rennin, valvular heart disease, venous plasma sampling

1. Introduction

Excess aldosterone secretion plays a key role in raising blood pressure in many patients, and not only in those who have primary aldosteronism, but also in a multitude of patients with low-renin primary (formerly termed "essential") hypertension and those with hypertension associated with overweight obesity.[1] In many such patients, current imaging techniques fail to allow identification of adrenocortical pathologies and only adrenal vein sampling (AVS) permits identification of lateralized aldosterone excess.[2–4] More recently an elevation in aldosterone levels was also reported in hypertensive patients with atrial fibrillation (AF).[5–7] However, whether aldosterone is elevated in normotensive patients with AF or other cardiac conditions is unknown. Furthermore, it is unclear whether alterations of the aldosterone-renin ratio (ARR) exist in unselected cardiac patients undergoing cardiac catheterization.

The present study undertook to prospectively measure plasma renin and aldosterone concentrations and the ARR in unselected patients undergoing cardiac catheterization with the intent of addressing the following questions: (i) Is there an elevation in aldosterone in various cardiac diseases/conditions? (ii) Can we reproduce, in this special patient population, the previously

Editor: Abdelouahab Bellou.

Funding: This work was partially funded by the Stiftung für Herz-und Kreislaufkrankheiten (to PE and TJR) which played no role in either study design, data analysis or manuscript preparation.

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:25(e7282)

Received: 6 February 2017 / Received in final form: 1 June 2017 / Accepted: 2 June 2017

http://dx.doi.org/10.1097/MD.0000000000007282

reported findings of aldosterone elevation in hypertension? (iii) Is AF a state of aldosterone elevation due to hypertension or is it independent of hypertension?

We measured aldosterone and active renin levels in a large cohort of patients and evaluated the associations of hormonal elevations in relation to specific and different cardiac diseases.

2. Patients and methods

The study was approved by the ethical committee of the Lucerne (Study Number 12032) and was conducted in compliance with the Declaration of Helsinki. All subjects provided written informed consent.

We studied patients in whom left heart catheterization did not yield a clear explanation for their symptoms and their heart disease could not be unambiguously established noninvasively. The patients underwent a right heart catheterization after overnight fasting and without any medication for least 12 to 24 hours. Blood was withdrawn on the venous side from patients in the supine position. Catheterization and blood withdrawal procedures were never performed during the week-end or in the emergency unit.

Blood sampling for plasma aldosterone concentration (PAC) and renin was taken from the renal vein during catheterization. Catheters used included a Judkins right heart catheter, a multipurpose catheter, or an Amplatz III catheter. Blood samples (4 mL) were drawn into EDTA vacutainer tubes, processed for preparation of cell-free plasma in the central laboratory of the hospital. Plasma samples were sent to Viollier AG (Allschwil, Switzerland) for analysis of renin and aldosterone.

Aldosterone and renin measurements were performed using validated LIAISON Aldosterone and LIAISON direct active renin concentration (DRC) commercial (DiaSorin) assay kits (Diasorin Switzerland AG, Rotkreuz, Switzerland). Measurements were performed on a LIAISON XL Analyzer.[7] Inter-assay and intra-assay coefficients of variability (CV) for renin determination are between 2.1–2.4% and 6.8–7.3%, respectively. Inter-assay CV and intra-assay CV for aldosterone determination are between 1.8–3.5% and 5.6–9.5% respectively. The elevation of renin was defined as a level > 33.5 mU/L and that of aldosterone as > 0.45 nmol/L. The elevation of aldosterone–renin ratio (ARR) was considered if it was > 0.14 nmol/L/mU/L.

Cardiac disease characterization was made after right heart catheterization. Hypertension was defined if blood pressure was above 150/90 mm Hg and it was recorded in medical history or the patient was treated for it. In the absence of ARR elevation or dynamically relevant renal arterial stenosis, the hypertension was attributed to primary (formerly called essential) hypertension. Hypertensive cardiomyopathy was defined if hypertension was present during catherization and coronary arteries were thickened and stenosis of the renal arteries was observed. AF was diagnosed if present at the time of catheter investigation or if an AF episode of at least 2 minutes duration was detected by 7-day continuous Holter ECG monitoring. Valvular heart disease was named moderate or severe according to the need of valvular replacement. Coronary artery disease (CAD) was established if there was coronary stenosis of 50% or more in at least 1 coronary vessel. Patients had either sinus rhythm or permanent or paroxysmal AF. Pulmonary hypertension was established if mean pulmonary artery pressure was > 25 mm Hg. Hypertensive cardiomyopathy was established if there was LV hypertrophy and there were signs of hypertension, inclusion of coronary artery disease, or any other conditions that might explain symptoms which were not answerable after left heart catheterization. Valvular heart disease was established if one of the heart valves was regurgitated or stenotic.

2.1. Statistical analysis

The analysis included all patients, and the patients were grouped according to the following cardiac diseases: hypertension, AF, pulmonary hypertension, hypertensive cardiomyopathy, CAD, valvular disease, LVEF below 35%. The results are presented as percentages for categorical variables and analyzed using the Pearson chi-square test or Fisher's exact test as appropriate. Continuous variables are expressed as median and interquartile ranges (IQR) and analyzed using the Mann-Whitney *U* test. $P < .05$ was taken as level of statistical significance. IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY) was used for statistical analyses.

3. Results

A total of 833 patients underwent left heart catheterization due to different cardiac diseases between February 2009 and March 2015. The most frequent diagnoses were hypertension (56.2%) and CAD (45%), followed by AF (20.4%), valvular heart disease (17.8%), and hypertensive cardiomyopathy (7.1%). Many patients had more than 1 diagnosis. The left ventricular ejection fraction (LVEF) was below 35% in 45 of 796 catheterized patients (in 37 of the 833 LVEF could not be calculated). The mean pulmonary artery pressure was above 25 mm Hg in 237 patients.

Figure 1 presents a numerical flow chart of the patient grouped according to specific cardiac disease conditions.

Aldosterone values were available for all patients (n = 833). Aldosterone was elevated in 272 patients (32.7%) with a median value of 0.82 nmol/L (IQR 0.59 – 1.31 nmol/L). Renin values were available for 826 patients. Renin was elevated in 228 patients (27.4%) with a median value of 77.95 mU/L (IQR 47.4–150.4 mU/L). The percentages of patients with elevated aldosterone, renin, and ARR are given in Table 1.

Hyperaldosteronism occurred in around one-third of all examined patients, without significant differences between patients with or without the named cardiac diseases. Trends only were noted in patients with impaired LVEF ($P = .074$) (Table 1).

Renin was significantly elevated in patients with hypertension, with CAD, and in patients with impaired LVEF (Table 1). Renin levels were on average 2-fold higher in hypertensive patients than in patients without hypertension (21.3 mU/L IQR 9.6, 53.3 mU/L vs 11.6 IQR 7.0, 20.9 mU/L; $P < .001$). Patients with CAD had also higher renin levels than patients without CAD (20.1 mU/L, IQR 10.5, 47.2 mU/L vs 11.8 mU/L IQR 6.6, 30.1 mU/L; $P < .001$). Patients with impaired LVEF had higher renin levels than patients with normal LVEF of 26.4 mU/L (IQR 10.4, 129.4 mU/L) versus 14.0 mU/L (IQR 7.0, 33.5; mU/L; $P < .001$).

ARR was significantly elevated in patients with AF ($P = .034$) and hypertensive cardiomyopathy ($P = .005$) compared to the patients without AF and hypertensive cardiomyopathy, respectively (Table 1).

Patients with AF and coexisting hypertension had a 2-fold higher prevalence of elevated renin than AF patients without coexisting hypertension (35.3% vs 16.5%; $P = .005$). Aldosterone elevation was not different between these patient groups

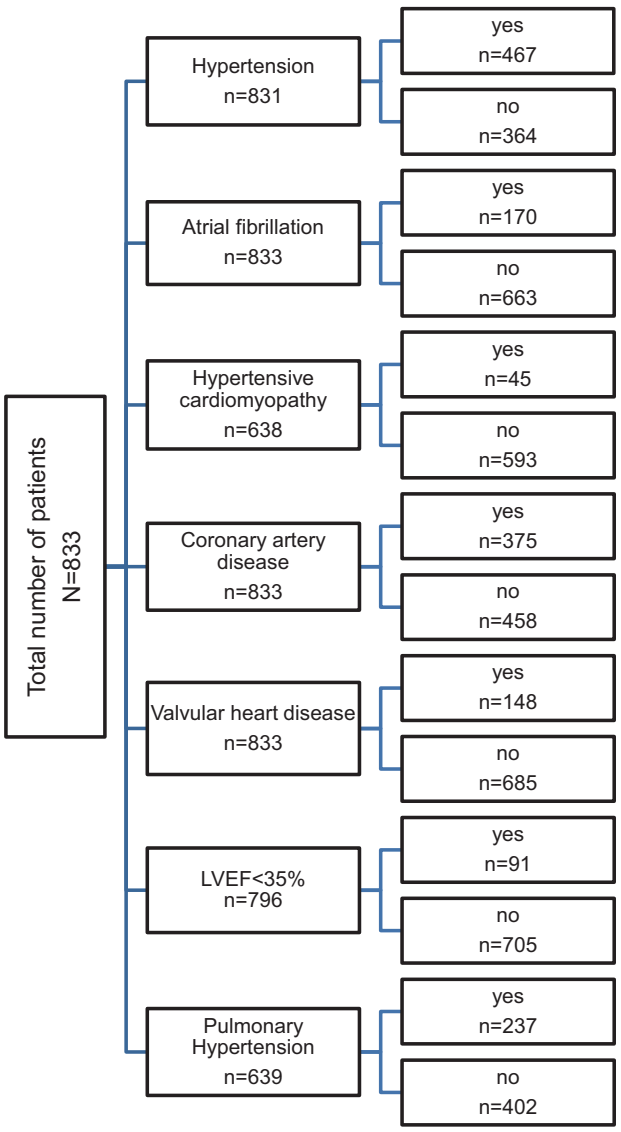

Figure 1. Numerical flow chart of patient grouping according to the cardiac disease condition.

(35.3% vs 40.0%; $P=.53$). Additionally, more patients with persistent or permanent AF had elevated renin levels than patients with paroxysmal AF (34.1% vs 15.8%; $P=.007$). Aldosterone elevation was also not different between these 2 patient groups (36.4% vs 41.3%; $P=.52$).

4. Discussion

To the best of our knowledge this is the first prospective study to have measured plasma aldosterone and active renin concentrations in a relatively large population of patients submitted to cardiac catheterization. In such patients, and particularly in those with severe LV dysfunction, liver synthesis of angiotensinogen can be limited, thus biasing the assessment of renin by means of plasma renin activity, the most widely used renin assay of the past decades. Of note, the direct sandwich assay of active renin concentration (LIAISON DRC) renders the assessment of plasma active renin totally independent of renin substrate availability and therefore provides a far more accurate measurement of renin in these types of patients.

Table 1

Percentages of patients with elevated aldosterone, renin, or aldosterone-renin ratio: comparisons between patients without and with named cardiac diseases: analysis of all included patients.

Hypertension	No	Yes	*P*
PAC elevated, %	128/364 (35.2)	144/467 (30.8)	.19
Renin elevated, %	58/364 (15.9)	170/467 (36.4)	<.001
ARR elevated, %	15/351 (4.3)	12/467 (2.6)	.18
Hypertensive cardiomyopathy	No	Yes	*P*
PAC elevated, %	201/593 (33.9)	12/45 (26.7)	.32
Renin elevated, %	178/593 (30.0)	13/45 (28.9)	.87
ARR elevated, %	13/584 (2.2)	4/42 (9.5)	.005
Atrial fibrillation	No	Yes	*P*
PAC elevated, %	208/663 (31.4)	64/170 (3726)	.12
Renin elevated, %	184/663 (27.8)	44/170 (25.9)	.63
ARR elevated, %	17/650 (2.6)	10/170 (5.9)	.034
Coronary artery disease	No	Yes	*P*
PAC elevated, %	140/458 (30.6)	132/375 (35.2)	.16
Renin elevated, %	101/458 (22.1)	127/375 (33.9)	<.001
ARR elevated, %	20/447 (4.5)	7/373 (1.9)	.038
Valvular heart disease	No	Yes	*P*
PAC elevated, %	223/685 (32.6)	49/148 (33.1)	.90
Renin elevated, %	179/685 (26.1)	49/148 (33.1)	.084
ARR elevated, %	24/676 (3.6)	3/144 (2.1)	.37
Left ventricular ejection fraction <35%	No	Yes	*P*
PAC elevated, %	221/705 (31.3)	37/91 (40.4)	.074
Renin elevated, %	175/705 (24.8)	43/91 (47.3)	<.001
ARR elevated, %	21/696 (3.0)	2/91 (2.2)	.66
Pulmonary hypertension (atrial pulmonary mean pressure >25 mm Hg	No	Yes	*P*
PAC elevated, %	125/402 (31.1)	75/237 (31.6)	.86
Renin elevated, %	108/402 (26.9)	68/237 (28.7)	.62
ARR elevated, %	8/397 (2.0)	9/231 (3.9)	.16

ARR = angiotensin-renin ratio, PAC = plasma aldosteron concentration.

Not unexpectedly, considering that renin is a potent pressor hormone, we found that the proportion of patients with elevated plasma active renin was higher among the patients with arterial hypertension. Moreover, it was higher also among those with CAD and with impaired LV ejection fraction, which is consistent with the notion that activation of the renin-angiotensin-aldosterone-system (RAAS) accelerates atherogenesis and that severe LV systolic dysfunction implies an activation of the RAAS because of under filling.[8]

A further important finding of this study concerns the observation that the ARR was elevated in the patients with AF and hypertensive cardiomyopathy. This occurred because PAC was elevated more than active renin. Although the elevation of PAC did not achieve statistical significance, the finding indicates the ARR provides a better assessment of the volume status and thus of atrial stretch. Notably, an elevation in aldosterone occurred in around one-third of all the examined patients with cardiac diseases. Patients with either valvular heart disease or elevated pulmonary arterial pressures did not show any differences regarding the presence of hyperaldosteronism or hyperrenism compared to patients without such conditions. These findings prompt a recommendation for the clinical practice to consider and search for the presence of hyperaldosteronism in patients with hypertensive heart disease and atrial fibrillation, but not in patients with CAD or valvular heart disease and elevated pulmonary artery pressure.

The high prevalence of hyperrenism and hyperaldosteronism in the patients with hypertension and with hypertensive cardiomyopathy causing AF is an important novel finding, in as much as

excess PAC in the setting of a high sodium intake has been associated with cardiac inflammation, scars, and myocardial remodeling, all changes that can create the stage for re-entry mechanisms and thus AF.[9–11] The finding is consistent with results from investigations on patients with primary aldosteronism in whom a high frequency of AF was found using retrospective [12] and prospective [13] study designs. Furthermore, it is also in accordance with the report of a relationship of excess PAC with LV hypertrophy, regardless of the elevation of blood pressure.[14]

4.1. Limitations of the study

There are several limitations to be acknowledged in this study. We could not ascertain what proportion of the hypertensive patients with elevated ARR had primary aldosteronism. This is because after having gone cardiac catheterization, they were referred back to their attending physician, and therefore not submitted to the necessary follow-up. Although much care was taken to obtain right and left adrenal venin blood we could not establish selectivity of the AVS, and therefore could not calculate the lateralization index and establish lateralized PAC excess. Lastly, some of the patients could not be studied after withdrawal of the drugs affecting the RAAS and the ARR. However, our results remained essentially unchanged after a sensitivity analysis that excluded the patients on beta blockers, the drugs that most affect the ARR.

5. Conclusions

In summary, this large prospective study of consecutive cardiac disease patients referred for cardiac catheterization has documented distinct differences with regard to the presence of elevations in plasma renin, PAC, and the ARR. The patients with arterial hypertension, CAD, and severe LV systolic atrophic dysfunction had a higher rate of hyperreninism. The higher proportion of hypertensive patients with hyperrenism, in particular those who also had AF, suggests that several cases of primary aldosteronism were likely concealed in these groups. Overall, our findings are consistent with the contention that regardless of renin, aldosterone excess adversely affects LVH and atrial remodeling thereby setting the pathological stage for arrhythmia, including atrial and possibly ventricular fibrillation. This could explain, at least in part, the reported reductions in death, including sudden death, in large clinical trials using mineralocorticoid receptor antagonists.[15,16]

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